IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Hang-Chiung LIN et al.	Confirmation No: 8466
Appl. No.	: 10/717,559	
Filed	: November 21, 2003	
Title	: PHARMACEUTICAL COMPOSITION FOR ENHANCING IMMUNITY, AND EXTRACT OF PORIA	
TC/A.U.	: 1617	
Examiner	: C.K. Huynh	
Docket No.:	: LINH3023/REF	
Customer No:	: 23364	

37 CFR § 41.37 APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This appeal brief is submitted with the required appeal fee set forth in §41.20(b)(2) of $500.00. Any additional fees necessary for this appeal may be charged to Deposit Account No. 02-0200.

The period for filing this appeal brief has been extended to expire on July 10, 2008, by the filing herewith of a Petition for a two-month extension of time and payment of the required fee.

41.37 (c)(1)(i) REAL PARTY IN INTEREST

The real party in interest is the Assignee of record, Sinphar Pharmaceutical Co. Ltd., Taiwan.

41.37 (c)(1)(ii) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences with respect to the claimed invention which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal known to appellant, appellant's legal representative or assignee.

41.37 (c)(1)(iii) STATUS OF THE CLAIMS

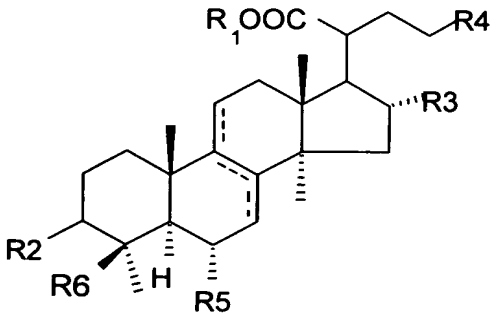
This application contains claims 1-23. Claims 1-5 and 14-23 have been canceled from the application without prejudice or disclaimer and are no longer pending. Claims 6-13 are pending and are the claims on appeal. Claims 6-13 stand finally rejected under 35 USC 103(a) as obvious over the prior art cited and applied in the Final Rejection.

41.37 (c)(1)(iv) STATUS OF AMENDMENTS AFTER FINAL REJECTION

No amendment after final rejection has been filed. The status of the claims is as finally rejected.

41.37 (c)(1)(v) SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 relates t a Poria extract capable of enhancing immunity of a mammal comprising 5-60% of a lanostane having the following chemical formula (I) by weight of the extract, and being substantially devoid of secolanostane:



(I)

wherein R_1 is either H or CH_3; R_2 is $OCOCH_3$, =O or OH; R_3 is H or OH; R_4 is $-C(=CH_2)-C(CH_3)_2R_a$, wherein R_a is H or OH, or $-CH=C(CH_3)-R_b$, wherein R_b is CH_3 or CH_2OH; R_5 is H or OH; and R_6 is CH_3 or CH_2OH. Page 6, lines 1-14

Claim 7 claims the extract which is prepared by a method comprising the following steps:

a) extracting metabolites, fermentation products or sclerotium of Poria cocos (Schw) Wolf by water, methanol, ethanol, or a mixed solvent thereof;

b) concentrating the resulting liquid extract from step a);

c) introducing the resulting concentrated substance from step b) into a silica gel column;

d) eluting the silica gel column with an eluent having a low polarity, and collecting the resulting eluate;

e) concentrating the eluate to form a concentrated eluate,

wherein the concentrated eluate from step e) has a chromatographic value, Rf, not less than 0.1 in accordance with a thin layer chromatography, which is developed by a mixed solvent of dichloromethane : methanol = 96:4 and is detected by an ultraviolet lamp and iodine vapor. See page 6, line 13 to page 7, line 5.

41.37 (c)(1)(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

THERE ARE TWO OBVIOUSNESS REJECTIONS

The first obvious rejection to be reviewed is of claims 6-13 under 35 U.S.C. 103(a) as being unpatentable as obvious over Takahashi et al. (JP 8-119864) in view of Tai et al. (Phytochemistry. 1995. Vol. 39, No. 5. pp. 1165-1169).

The second obvious rejection to be reviewed is of claims 6-13 under 35 U.S.C. 103(a) as being unpatentable as obvious over Babish et al. (US 2002/0068098) in view of Cuellar et al. (Chemical and Pharmaceutical Bulletin. 1997. Vol. 45, No. 3. pp. 492-494) and Tai et al. (Phytochemistry. 1995. Vol. 39, No. 5. pp. 1165-1169).

41.37 (c)(1)(viii) ARGUMENT

CLAIM INTERPRETATION AND REQUIREMENTS FOR AN OBVIOUSNESS REJECTION

As noted in MPEP § 2141.02, ascertaining the differences between the prior art and the claims at issue requires interpreting the claim language and considering both the invention and the prior art reference as a whole. In determining the differences between the prior art and the claims, the question under 35 USC 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. It is further noted in this section that a patentable

invention may lie in the discovery of the source of a problem even thought the remedy may be obvious once the source of the problem is identified. This is part of the subject matter as a whole which should always be considered in the determination of the obviousness of an invention under 35 USC 103.

As noted on page 18 of Appellants' specification, the potent component of the Poria extract is a lanostane-containing low polarity portion, which is capable of enhancing immunity of the human body. It is further stated that the Poria extract obtained by the method of the present invention is devoid of the inhibitive components, which are secolanostanes and higher polarity molecules contained in the high polarity portion, PCW_E. For this reason the method and the resulting claimed extract is unobvious. That is, part of the invention as a whole is the recognition of the adverse effects of the secolansotanes and restricting the claimed extract to being substantially devoid of secolansotanes. The present specification contains experimentation, both in vitro and in vivo, in support of these limitations. Appellants also most respectfully direct the Examiner's attention to MPEP § 2144.08 (page 2100-130) wherein it is stated that Office personnel should consider all rebuttal argument and evidence present by applicant and the citation of In re Soni for error in not considering evidence presented in the specification.

On page five of the Final Rejection, it is urged that claims 6-13, the claims on appeal, are drawn to a Poria extract and thus intended use is not given any patentable weight. The recitation, "enhancing immunity" has not been given patentable weight because the recitation occurs in the preamble. It is stated further that a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. With respect to the presently claimed subject matter, these statements are specifically traversed for the reasons set forth in MPEP §2111.02, Effect of Preamble. Clearly, one of ordinary skill in the art is familiar with extracts as would be evident from the specification of the present application. On page

three, line 16, it is noted that the method of the present invention makes use of the conventional extraction process, by means of which a crude extract is obtained. Of course this extract is further treated to arrive at the presently claimed extract. The claims on appeal are to an extract and not to the individual compounds per se. The extract is an integral part of the claim which breathes life into the claim and it is improper to ignore this claim limitation in determining the obviousness of the claimed extract.

This is similarity true with respect to the recitation, "enhancing immunity" which relates to the structural composition of the extract and the removal of the of the adverse effects of the secolansotanes by restricting the claimed extract to being substantially devoid of secolansotanes as demonstrated by the test results in Appellants' specification.

Examples Of Basic Requirements of a Prima Facies Case of Obviousness

The appellant submits that the criteria set forth in the MPEP provides guidance in determining the issue of obviousness of the claims on appeal.

---SECTION---2143 Examples Of Basic Requirements of a Prima Facie Case of Obviousness

The Supreme Court in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit.

SECTION---2143.03 All Claim Limitations Must Be Taught or Suggested

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against

the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Appellants note the Examiner's comments in the Final Rejection that any differences between the prior art would have been obvious to one of ordinary skill in the art as a routine modification of the product in the absence of a showing of unexpected results does not establish a prima facie case of obviousness. This statement is tantamount to the statement that the invention was well within the ordinary skill in the art which has been found to be insufficient. A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). **'">[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).<

THE FIRST OBVIOUSNESS REJECTION

The rejection of claims 6-13 under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al. (JP 8-119864) in view of Tai et al. (Phytochemistry. 1995. Vol. 39, No.5. pp. 1165-1169) should be withdrawn or reversed on appeal.

In the Final Rejection, page 6 it is urged that Takahashi et al. teach the extraction of the compound of formula 13 and the compound of formula 14, which reads on the

elected species in instant claim 13 where R_2 is CH_3COO (paragraph [0011]). Poria is extracted with methanol and the extract contains 0.6% lanostane compounds of formula (I) (paragraph [0011]). The resulting liquid extract was concentrated with reduced pressure, subjected to silica gel column chromatography, and eluted with chloroform and methanol (50:1) (paragraph [0011]).

It is recognized that Takahashi et al. do not teach the step of concentrating the eluate to form a concentrated eluate with thin layer chromatography (TLC) in the Final Rejection.

At page three of the Final Rejection and regarding Takahashi et al., examiner maintains and argues that Takahashi et al. teach at least one compound having a lanostane skeleton **or** a 3,4-secolanostane skeleton (page 5, paragraph [0001]). Accordingly, Takahashi et al. do teach a compound having a lanostane skeleton of formula (I). Polyporenic acid C, pachymic acid, and dehydropachymic acid are all appropriate lanostane compounds of formula (I) (pages 11-12, paragraph [0011]). The extraction method of Takahashi et al. yielded 33 mg of polyporenic acid C, 500 mg of pachymic acid, and 100 mg of dehydropachymic acid, for a total of 633 mg in 86.4 g of extract or 0.7% of the extract. It would be obvious that the extract may contain 5 to 60% of a lanostane compound of formula (I) because the skilled artisan would know how to optimize the extraction process to yield the appropriate amount of lanostane compounds of formula.

Appellants' most respectfully submit that this aspect of the rejection omitted a fact that the Poria extract prepared by Takashi contains 0.12% of secolanostane (formula 16, 100 mg in Fraction D). The Examiner acknowledge' that the extract prepared in this prior art contains only 0.73% of the compounds having the formula (I) recited in Claim 6. That is the extract taught by Takashi is different in the extract recited in claim 6 in the relatively amount of the compounds (I) and in the existence of secolanostane. Please note that no matter how the extract taught by Takashi is optimized the ratio of secolanostane (0.12%) to the compounds (I) (0.73%) should remain about 0.12/0.73, i.e. 16.4%. This high content of secolanostane in the extract

of the present invention and is contrary to the teaching of the subject invention to limit the amount of secolanostane. There is no motivation in the prior art to removing this aspect of the extract.

The inventors of the present application show the Poria extract (PCM-E Example 2, PCM in Example 1) comprising 5-60% of a lanostane by weight of the extract and being substantially devoid of secolanostane is capable of enhancing immunity of human body. The extract containing secolanostanes, PCW-E in Example 2, is shown to be inhibitive as to the immunity of human body. For this reason, the present invention is non-obvious over the extract disclosed by Takashi.

Further, Takashi teaches that secolanostane is also a potent component as shown in Example 2, [0050], where the compound of formula 16, a secolanostane, is 10% by weight of a 200 mg tablet. Tai et al., discloses purified compounds of lanostanes and secolanostane, and methods of purification. In view of these facts, there is lack of motivation to prepare a *Poria* extract comprising 5-60% of a lanostane by weight of the extract and being substantially devoid of secolanostane, when people ordinarily skilled in the art want to prepare a Poria extract which is capable of enhancing immunity of human body in view of Takashi and further in view of Tai et al.

In the Final Rejection it is urged that Tai et al. teach extraction of various lanostane compounds of formula (I) (page 1168). The extraction involves exposing the sclerotia of *Poria cocos* to methanol (page 1168). The liquid extract was dried and concentrated with Et_2O (pages 1168-1169). The resultant concentrated extract was introduced into a silica gel column with CHCl3 and MeOH-$CHCl_3$ gradient mixtures (page 1169). The extract was rechromatographed on a silica gel column with MeOH-$CHCl_3$ (page 1169). Purification was performed using TLC with MeOH-$CHCl_3$ (1:199) (page 1169).

To a person of skill in the art at the time of the invention, it would have been obvious to employ the lanostane (I) compounds of Takahashi et al. to undergo purification with TLC because the lanostane compounds of Tai et al. have undergone purification with TLC and according to Tai et al., the extraction of lanostane compounds

from *Poria cocos* includes the step of purification with TLC. However, this does not arrive at the presently claimed extract.

The motivation to combine the compounds of Tai et al. to the compounds of Takahashi et al. is that the compounds of Tai et al. are lanostane compounds that have undergone purification with TLC but this does not teach one of ordinary skill in the art the presently claimed invention.

The rejection of claim 7 does not stand or fall with the rejection of claims 6-13.

If the limitations of claim 6 is ignored as preamble, the limitation of claim 7 which specifies e) concentrating the eluate to form a concentrated eluate, wherein the concentrated eluate from step e) has a chromatographic value, Rf, not less than 0.1 in accordance with a thin layer chromatography, which is developed by a mixed solvent of dichloromethane : methanol = 96:4 and is detected by an ultraviolet lamp and iodine vapour cannot be ignored as preamble. As noted at the top of page 4 of the specification, The chromatographic value of the secolanostane fraction is small than 0.1. Therefore, secolanostane is not in the extract nor are cytotoxic properties associated with this component.

Regarding the chromatographic value, Rf, and the mixed solvent as recited in instant claim 8, the Final Rejection urges that it would be obvious to one skilled in the art at the time of the invention to change the solvent used and thus change the Rf value in order to meet the limitations of the claim. Solvents are routinely changed due to the polarity of the compounds to extract and the availability of the solvent. Because the solvents can be changed, the resulting Rf will also change. There is no suggestion as to any motivation to remove the secolanostane portion from the extract. Accordingly, it is most respectfully requested that this rejection be withdrawn or reversed on appeal.

THE SECOND OBVIOUSNESS REJECTION

The rejection of claims 6-13 under 35 U.S.C. 103(a) as being unpatentable over Babish et al. (US 2002/0068098) in view of Cuellar et al. (Chemical and Pharmaceutical Bulletin. 1997. Vol. 45, No. 3. pp. 492-494) and Tai et al. (Phytochemistry. 1995. Vol. 39, No. 5. pp. 1165-1169) should be withdrawn or reversed on appeal.

It is urged that Babish et al. teach a composition comprising pachymic acid, a triterpene, which reads on the elected species in instant claim 2 where R_2 is CH_3COO (page 3, Table 1). The composition contains preferably greater than 50% triterpene by weight (page 5, paragraph [0038]). The composition is given in capsule or tablet form to an adult human (page 5, paragraph [0045]).

Babish et al. do not teach an extraction method for a lanostane of formula (I), the step of eluting the silica gel column with an eluent having low polarity, and the step of concentrating the eluate.

Cuellar et al. teach extraction of pachymic acid from *Poria cocos* (page 494), The extraction involves, first, extracting metabolites from the sclerotium of *Poria cocos* with 50% aqueous ethanol (page 494). The extract was then concentrated with reduced pressure (page 94). The resultant concentrated extract was introduced into a silica gel column with a mixture of $CHCl_3$/EtOAc to yield pachymic acid (page 494). Identification of pachymic acid was performed with ^3H- and ^{13}C-NMR spectral analysis (page 494). Moreover, Cuellar et al. teach that Hoelen or *Poria cocos* extract has a remarkable inhibitory effect on the secretion of the cytokines IL-1β, IL-6, TNF-α, and GM-CSF as well as having a protective effect on stress- induced ulcers (page 492). Thus it would be obvious that the lanostane compounds of formula (I) may be used to enhancing immunity in mammals but this is not the claimed invention. There is no suggestion of removing the secolanostane from the extract to arrive at the presently claimed extract.

Tai et al. teach extraction of various lanostane compounds of formula (I) (page 1168). The extraction involves exposing the sclerotia of *Poria cocos* to methanol (page 1168). The liquid extract was dried and concentrated with Et_2O (pages 1168-1169). The

resultant concentrated extract was introduced into a silica gel column with $CHCl_3$ and MeOH-$CHCl_3$ gradient mixtures (page 1169). The extract was rechromatographed on a silica gel column with MeOH-$CHCl_3$ (page 1169). Purification was performed using TLC with MeOH-$CHCl_3$ (1:199) (page 1169).

To a person of skill in the art at the time of the invention, it would have been obvious to employ the lanostane (I) compounds of Babish et al. to undergo extraction from *Poria cocos* because the lanostane (I) compounds of Cuellar et al. and Tai et al. have undergone extraction from *Poria cocos* and according to Cuellar et al. and Tai et al., lanostane (I) compounds can be extracted from *Poria cocos*.

The motivation to combine the compounds of Cuellar et al. and Tai et al. to the compounds of Babish et al. is that the compounds of Cuellar et al. Tai et al. are lanostane (I) compounds that have been extracted from *Poria cocos*.

Appellants wish to note that Babish et al. teach a composition comprising pachymic acid among other compounds listed in Table 1, col. 3. Please note that pachymic acid is not the preferred compound and there are so many compounds in Table 1. Please note that the claimed subject matter of claim 6 is a Poria extract, that means a composition containing nature compounds extract from Poria in addition to the lanostane compounds (I). Therefore, no matter how the composition of Babish et al. is purified it is impossible to have a composition having nature compounds extract from Poria. Appellants also wish to emphasize that a composition comprising pachymic acid is not a Poria extract, just like a purified water containing added minerals is not a mineral water. Even Cuellar et al. discloses a method of purifying pachymic acid and Tai et al. discloses a method of purifying pachymic acid, they can only help Babish et al. in preparing a composition comprising pachymic acid. Another question is why people want to prepare a composition comprising purified pachymic acid from the composition comprising pachymic acid among other compounds listed in Table 1, col. 3 disclosed by Babish et al.

Please note that Tai et al use TLC to prepare purified lanostane compounds (I), not using TLC to prepare a Poria extract containing 5-60% of a lanostane by weight of

the extract and being substantially devoid of secolanostane. Therefore, even Takashi undergoes purification with TLC as suggested by Tai et al, there is still lack of motivation to use TLC to exclude secolanostane in preparing a Poria extract. Accordingly, it is most respectfully requested that this rejection be withdrawn or reversed on appeal.

The rejection of claim 7 does not stand or fall with the rejection of claims 6-13.

If the limitations of claim 6 is ignored as preamble, the limitation of claim 7 which specifies e) concentrating the eluate to form a concentrated eluate, wherein the concentrated eluate from step e) has a chromatographic value, Rf, not less than 0.1 in accordance with a thin layer chromatography, which is developed by a mixed solvent of dichloromethane : methanol = 96:4 and is detected by an ultraviolet lamp and iodine vapour cannot be ignored as preamble. As noted at the top of page 4 of the specification, The chromatographic value of the secolanostane fraction is small than 0.1. Therefore, secolanostane is not in the extract nor are cytotoxic properties associated with this component.

Regarding the chromatographic value, Rf, and the mixed solvent as recited in instant claim 8, the Final Rejection urges that it would be obvious to one skilled in the art at the time of the invention to change the solvent used and thus change the Rf value in order to meet the limitations of the claim. Solvents are routinely changed due to the polarity of the compounds to extract and the availability of the solvent. Because the solvents can be changed, the resulting Rf will also change. There is no suggestion as to any motivation to remove the secolanostane portion from the extract. Accordingly, it is most respectfully requested that this rejection be withdrawn or reversed on appeal.

IX. CONCLUSION

In view of the above arguments, all of the rejections of the claims on appeal should be withdrawn or reversed. The application should be passed to issue.

Respectfully submitted,

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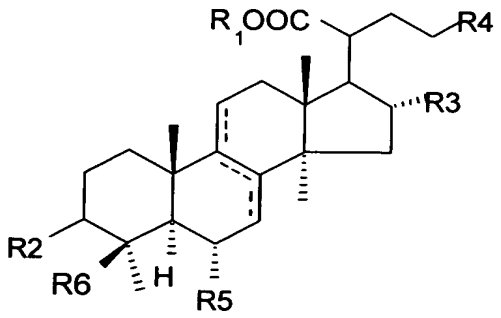
REF:cjw
Appeal Brief D3.wpd

July 10, 2008

41.37 (c)(1)(viii) Claims appendix

6. A Poria extract capable of enhancing immunity of a mammal comprising 5-60% of a lanostane having the following chemical formula (I) by weight of the extract, and being substantially devoid of secolanostane:



(I)

wherein R_1 is either H or CH_3; R_2 is $OCOCH_3$, =O or OH; R_3 is H or OH; R_4 is $-C(=CH_2)-C(CH_3)_2R_a$, wherein R_a is H or OH, or $-CH=C(CH_3)-R_b$, wherein R_b is CH_3 or CH_2OH; R_5 is H or OH; and R_6 is CH_3 or CH_2OH.

7. The Poria extract according to claim 6, which is prepared by a method comprising the following steps:

a) extracting metabolites, fermentation products or sclerotium of Poria cocos (Schw) Wolf by water, methanol, ethanol, or a mixed solvent thereof;

b) concentrating the resulting liquid extract from step a);

c) introducing the resulting concentrated substance from step b) into a silica gel column;

d) eluting the silica gel column with an eluent having a low polarity, and collecting the resulting eluate;

e) concentrating the eluate to form a concentrated eluate.

8. The Poria extract according to claim 7, wherein the concentrated eluate from step e) has a chromatographic value, Rf, not less than 0.1 in accordance with a thin layer chromatography, which is developed by a mixed solvent of dichloromethane : methanol = 96:4 and is detected by an ultraviolet lamp and iodine vapor.

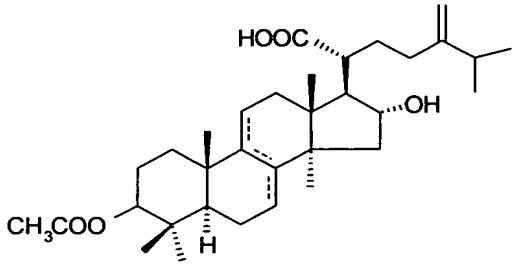
9. The Poria extract according to claim 7, wherein the extraction in step a) is carried out by using 95% ethanol.

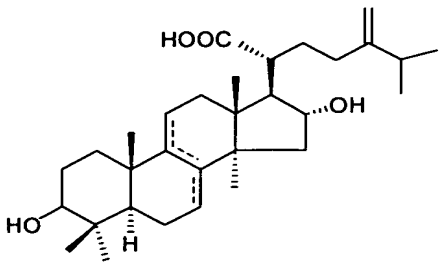
10. The Poria extract according to claim 7, wherein the concentrated substance resulted from step b) is further extracted with a two-phase solvent containing methanol and n-hexane in a volumetric ratio of 1:1, a methanol layer is separated from the two-phase solvent extraction mixture, and the methanol layer is concentrated to form a concentrate, which is used as a feed to the silica gel column in step c).

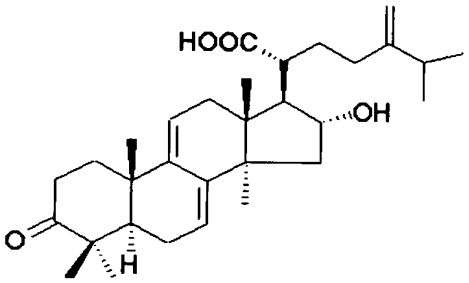
11. The *Poria* extract according to claim 7, wherein the low polarity eluent is a mixed solvent containing dichloromethane and methanol in a volumetric ratio of 96.5:3.5.

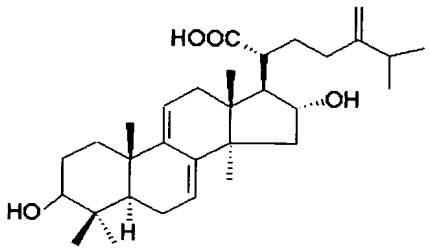
12. The *Poria* extract according to claim 6 comprising 10-20% of the lanostane (I).

13. The *Poria* extract according to claim 6, wherein the lanostane (I) is









or

41.37 (c)(1)(ix) Evidence appendix

NONE

41.37 (c)(1)(x) Related proceedings appendix

None